923-67 Bronchial Hyperresponsiveness (BHR) in Congestive Heart Failure (CHF) May Be Mediated by Impairment of the Pulmonary Adrenergic Signal Transduction Pathway

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Wheezing often aggravates the clinical symptoms of CHF. Part of this BHR may be mediated by vascular congestion and vagal reflexes. Changes of the adrenergic signal transduction pathway in the lung may add to the clinical symptoms, but they have not been investigated so far. To clarify whether an impairment of β-adrenergic signal transduction pathway might contribute to BHR in CHF, the adrenergic signal transduction system was studied in rats 4 weeks after aortic banding. At that time, LVEDP (11 ± 1 vs. 5 ± 1 mmHg), lung wet weight (1968 ± 199 vs. 1216 ± 74 mg), and plasma norepinephrine levels (0.56 ± 0.10 vs. 0.34 ± 0.06 nM) had increased significantly. Beta-adrenergic receptor densities (βAR) and affinities (K_D) were determined in pulmonary plasma membrane preparations by radioligand binding assays using [^{125}I]Iodocyanopindolol. Compared to sham-operated controls (n = 8), βAR were decreased in CHF (n = 9) to 585 ± 44 vs. 791 ± 101 fmol/mg protein ($p < 0.05$). The densities of βAR were negatively related to lung wet weight ($r = -0.71$, $p < 0.05$). K_D values remained unchanged (25 ± 3 vs. 20 ± 3 pM). Receptor-independent, sodium-fluoride stimulated adenylyl cyclase activity in lung membranes was decreased by 28% ($p < 0.05$) in CHF. On a functional level, the isoproterenol-induced relaxation of isolated tracheal rings precontracted with carbachol was also significantly blunted when compared to controls.

Conclusions: These data demonstrate for the first time that neuroendocrine activation in CHF is associated with a downregulation of pulmonary β-adrenergic receptors and of pulmonary adenylyl cyclase activity, leading to an impaired response of airway smooth muscle to adrenergic stimuli. Thus, BHR in CHF may be in part due to a reduction in β-adrenergic bronchodilatory tone and contribute to the clinical manifestation of "cardiac asthma".

923-68 Chronically Infarcted Hearts Exhibit Increased Susceptibility to High-Workload — but Not to Low-Workload — Metabolic Stress

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In residual intact myocardium of chronically infarcted hearts, energy reserve via creatine kinase is reduced: Total creatine kinase, total creatine and creatine kinase reaction velocity are all reduced by up to 50%. For hearts of transgenic mice with a null-mutation of the creatine kinase-M gene, susceptibility to ischemia/reperfusion is unchanged, but susceptibility to high-dose isoproterenol is increased. We tested whether this is also true for failing chronically infarcted hearts. Two months following infarction (MI) or sham operation, rat hearts were isolated and buffer-perfused isovolumically with end-diastolic pressure set to values measured before *in vivo*. ^{31}P-NMR spectra were obtained in 5 min intervals at 7 Tesla. In protocol 1, hearts (sham: n = 10, MI: n = 5) were subjected to 15 min of total global ischemia followed by reperfusion. During ischemia and reperfusion, changes of ATP (end of ischemia: 3.7 ± 0.3 mM in sham, 3.8 ± 0.4 mM in MI hearts), phosphocreatine (Reperfusion: 11.3 ± 0.8 mM in sham and 11.4 ± 1.4 mM in MI hearts) and mechanical performance were similar. In protocol 2, sham (n = 10) and MI hearts (n = 6) were subjected to isoproterenol-infusion at increasing dosages (10, 100, 250 ng/min). Here, increases of rate-pressure products were similar for sham and MI; however, during inotropic stimulation, phosphocreatine depletion was greater in infarcted hearts (PCr: 64 ± 3% of control at 250 ng/min) than in sham (PCr: 79 ± 2%; *$p < 0.005$). Conclusion: Similar to creatine kinase-M-deficient hearts, chronically infarcted hearts with reduced energy reserve via creatine kinase show unaltered susceptibility to metabolic stress associated with low workload (ischemia/reperfusion), but increased susceptibility to metabolic stress associated with high workload (isoproterenol stimulation).

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Orange County Convention Center, Hall E
Presentation Hour: 3:00 p.m.–4:00 p.m.

924-69 The Relationships Between Endothelin-1 Secreted During Exercise and Pulmonary Vascular Tone in Patients With Mild Mitral Stenosis

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The purpose of this study is to clarify the relationships between plasma endothelin-1 (ET) secreted during exercise and the hemodynamic parameters in patients with mild mitral stenosis(MS).

We measured respiratory variables and determined the anaerobic threshold(AT) during ramp loading cycle ergometer of 15 patients with MS [MVA = 1.56 ± 0.51 cm^2, Pulmonary artery pressure(PPA)-systolic = 35.1 ± 8.3 *mmHg] and 4 normal subjects(control).* Arterial blood samples were obtained at rest (ET-rest) and 3 minutes after AT was recognized(ET-AT), and plasma concentrations of ET were measured using sandwich-type enzyme immunoassay. Hemodynamic parameters were obtained by cardiac catheterization. *Results:* 1), Both ET-rest and ET-AT in MS (1.11 ± 0.74, 1.30 ± 0.77 pg/ml) were significantly higher than in the control (0.62 ± 0.12, 0.66 ± 0.12, $p < 0.05$, respectively). 2), ET-AT were significantly increased than ET-rest in MS ($p < 0.05$). 3), The correlations between ET-rest, ET-AT or d-ET (ET difference between at rest and AT) and hemodynamic parameters in MS were as follows:

	ET-rest	ET-AT	d-ET
PPA-systolic	NS	$r = 0.57$ $p < 0.05$	$r = 0.55$ $p < 0.05$
PPA-mean	NS	$r = 0.56$ $p < 0.05$	$r = 0.59$ $p < 0.05$
TPRI	$r = 0.82$ $p < 0.001$	$r = 0.87$ $p < 0.001$	NS

Conclusion: These data suggest that not only an increase of ET at rest but also ET secreted during exercise at the AT level is implicated to increase of pulmonary vascular tone in patients with MS.

924-70 Absence of Functional Mitral Regurgitation (MR) Despite Severely Reduced Left Ventricular Function: Insights Into the Mechanism of MR

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Recent studies have suggested that global LV systolic dysfunction primarily determines functional MR. Clinical observations, however, suggest there are patients with severely reduced global function but no MR. We explored this observation by reviewing 1,366 consecutive patients studied by 2D echo and color Doppler with LV ejection fractions (EFs) < 30% (mean, 17.8 ± 6%), of whom 190 (14%) had no MR. We then randomly selected 34 patients, 17 with and 17 without MR, for quantitative analysis, including: LV EF by biplane Simpson's, LV internal diameters and sphericity ratio of short- to long-axis diameters; mitral annular size; MR jet area and proximal width; and the incomplete mitral leaflet closure (IMLC, tenting) area apical to the annulus (4-chamber). *Results:* LVEF was not significantly different between those without and with MR (17.8 ± 5.9 vs 17.7 ± 6.0%), as was age. Patients without MR had: 1) smaller LVs in systole (58 ± 9 vs 66 ± 8 mm, $p < 0.02$) and diastole (63 ± 10 vs 72 ± 6, $p < 0.005$); 24% vs 81% of pts without MR had systolic diameters > 60 mm ($p < 0.002$), and several had pericardial limitation; 2) lower LV sphericity in systole and diastole ($p < 0.007$); 3) smaller mitral annuli (40 ± 6 vs 45 ± 5 mm, $p < 0.03$); and 4) smaller IMLC areas (1.1 ± 0.5 vs 3.1 ± 1.4 cm^2, $p < 0.006$). Multiple linear regression showed that MR presence and amount correlated with both IMLC and LV sphericity ($r^2 = 0.64$), and the IMLC area correlated best with sphericity ($r^2 = 0.27$). *Conclusions:* MR may be absent despite severely reduced LV systolic function. Changes in LV size and shape correlate with functional MR, which is related to apical leaflet tenting, consistent with abnormal tethering by displaced attachments.

924-71 Effect of Acute Beta-Adrenergic Blockade on the Severity of Mitral Regurgitation in Chronic Canine Mitral Regurgitation

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Acutely, β-blockers precipitate decompensation in chronic mitral regurgitation